

Tetracyclic Triterpenes. Part 7.¹ Circular Dichroism of Some Steroid and Triterpenoid 5-En-7-ones; Conformational Aspects

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C.d. spectra of some steroid and triterpenoid 4,4-dimethyl-5-en-7-ones, showing long-wavelength $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ Cotton effects of opposite sign to those of ordinary 5-en-7-ones, are indicative of ring *B* conformations close to the two different sofa conformations: *S*(9 α) in the 9 α ,10 β -series and *S*(8 α) in the 9 β ,10 α -series.

Circular dichroism (c.d.) has proved a sensitive tool for studying conformations of cyclohexenones, including the large family of conjugated steroidal 4-en-3-ones (for recent accounts see refs. 2–5). Of particular interest are the changes in c.d. spectra that follow changes of configuration at C-10 and C-9.³ The conformational and chiroptical features of the ring *B* 5-en-7-ones have been explored to a much lesser extent.^{6,7} Recent progress in the synthesis of such enones as intermediates for transformation of lanosterol into cucurbitacins^{1,8} and resolving the need for knowledge of their stereochemistry have prompted us to report the c.d. spectra in the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition range.

In our analysis we will utilize the well established concept of the relation of the $n \rightarrow \pi^*$ and long-wavelength $\pi \rightarrow \pi^*$ Cotton effects (at 300–350 and 230–250 nm, respectively) to the helicity of the enone system (*i.e.* non-coplanarity of the C=C and C=O groups)^{2,3,9,10} as well as the recently formulated dependence of the short-wavelength $\pi \rightarrow \pi^*$ Cotton effect (at *ca.* 200–220 nm) upon the absolute configuration and conformation of the cyclohexenone ring.³ (For alternative interpretations of the structural dependence of the short-wavelength $\pi \rightarrow \pi^*$ Cotton effect see ref. 4 and references cited therein.) In order to obtain a more reliable conformational picture, supplementary ¹H n.m.r. and X-ray data will be discussed.

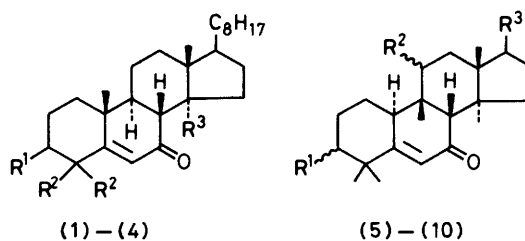
The results of the c.d. measurements on the new compounds are listed in the Table. Besides the 'normal' series compounds (1)–(4) (9 α ,10 β -configuration), the examples include the 9 β ,10 α -stereoisomers (5)–(10) and the 9 β ,10 β -stereoisomer (11). All these enones (4)–(11) contain the 4,4-dimethyl and 14 α -methyl substituents, which may additionally contribute to the conformational and c.d. characteristics. The effect of the 4,4-dimethyl system seems especially important, as numerous literature data indicate that the influence of 4,4-dimethyl substitution on the ring *A* conformation is rather sensitive to the overall stereochemistry of the skeleton. For example, it has been recently shown by X-ray analysis that in saturated 3-oxo-4,4-dimethyl-5 α -steroids, ring *A* adopts a flattened chair conformation, with less distortion in the 19-nor-series.¹¹ However, in the presence of the equatorial 6 α -hydroxy-group, ring *A* in 3-oxo-4,4-dimethylandrosterone assumes a fully staggered twist-boat conformation, intermediate between the C(2)–C(5) and C(3)–C(10) boat conformations, in which all potential non-bonded interactions are simultaneously minimised.¹² Flattening of ring *A* in 3-oxo-4,4-dimethyl steroids also accounts for the negative $n \rightarrow \pi^*$ Cotton effect of the 3-oxo-group. Similarly a ring *A* chair conformation in 3-oxo-4,4-dimethyl steroids is indicated by recent theoretical calculations and by lanthanoid-induced shift studies.¹³

Turning now to the Δ^5 -series we note that the olefinic bond lowers the energy difference between chair and boat forms, so

Table. C.d. data for 5-en-7-ones

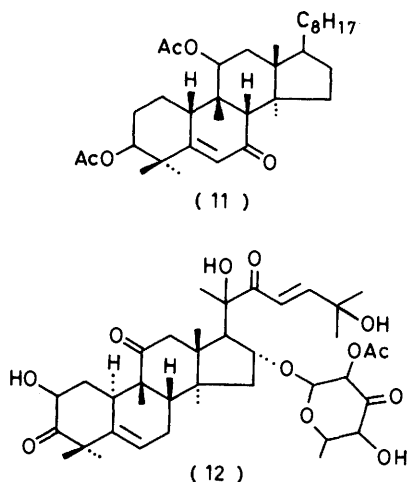
Compound	$n \rightarrow \pi^*$	C.d. $\Delta\epsilon$ (nm)	
		$\pi \rightarrow \pi^*$	
		Band 1	Band 2
(1)	–0.1 (373) +1.35 (333)	–12sh (232)	–16.0 (214)
(2)	–0.11 (385) +1.30 (336)	–7.6sh (235)	–13.1 (212)
(3)	–1.30 (355)	+1.2 (255)	–12.3 (218)
(4) ^a	–1.94 (343–355)	+7.6 (253)	–18.9 (225.5)
(5)	–1.04 (339)	+17.5 (242)	
(6)	–0.79 (340)	+16.4 (239)	
(7) ^b	–0.80 (339)	+17.2 (240)	
(8)	–0.82 (339)	+17.1 (240)	
(9) ^c	–0.53 (341)	+16.8 (236)	
(10) ^d	–0.98sh (337)	+12.2 (248)	
(11)	–0.89 (341)	+18.8 (238)	

^a Additional $n \rightarrow \pi^*$ Cotton effect due to the 11-oxo-group: +2.1 (294). ^b Additional $n \rightarrow \pi^*$ Cotton effect due to the 20-oxo-group: +3.5 (285). ^c Additional $n \rightarrow \pi^*$ Cotton effect due to the 11-oxo-group: +6.0 (298). ^d Additional Cotton effects due to the Δ^5 -3-oxo-group: –3.58 (293), –5.2 (216).



- (1) $R^1 = R^2 = R^3 = H$
 (2) $R^1 = OAc, R^2 = R^3 = H$
 (3) $R^1 = R^3 = H, R^2 = Me$
 (4) $R^1 = OAc, R^2 = R^3 = Me$ (11-oxo)
 (5) $R^1 = \beta-OH, R^2 = \beta-OH, R^3 = C_8H_{17}$
 (6) $R^1 = \beta-OAc, R^2 = \beta-OAc, R^3 = C_8H_{17}$
 (7) $R^1 = \beta-OAc, R^2 = \beta-OAc, R^3 = COMe$
 (8) $R^1 = \beta-OAc, R^2 = \beta-OAc, R^3 = C_4H_8CO_2Me$
 (9) $R^1 = \beta-OAc, R^2 = O, R^3 = C_8H_{17}$
 (10) $R^1 = O, R^2 = \beta-OAc, R^3 = C_8H_{17}$

that the 4 α -Me, 6-H interaction can drive the ring *A* conformational equilibrium towards the twist-boat conformation, as shown above for 6 α -hydroxy-4,4-dimethyl-3-ketones. Indeed, the twist-boat ring *A* conformation in 4,4-dimethyl-5-en-3-ones is also demonstrated by dipole moment and force-field calculations,¹⁴ as well as by X-ray analysis.¹⁵



The conformation of ring *B* in 5-en-7-ones with no additional substituents is of the sofa type, enantiomeric to the ring *A* conformation in unsubstituted 4-en-3-ones. Indeed, the c.d. spectra of (1)³ and (2) are of mirror-image type in relation to those of the corresponding 4-en-3-ones, thus suggesting the HC(8 β ,9 α)-S(9 α) ring *B* conformation (Figure), quasi-enantiomeric to the HC(1 α ,2 β)-S(1 α) ring *A* conformation³ (in the strain-free chair conformation of ring *A* the equatorial 3 β -acetoxy-group has little effect on the conformation of the 5-en-7-one system). On the other hand, the 4,4-dimethyl system has a pronounced effect on the c.d. spectra of the 5-en-7-one in (3) as compared with (1).³ This effect, essentially a reversal of the signs of the $n \rightarrow \pi^*$ and long-wavelength $\pi \rightarrow \pi^*$ Cotton effects, can be attributed to the interaction of the chromophore with the allylic bonds at C-4 and to the conformational change of ring *A* (see above), followed by a change of ring *B* conformation towards S(9 α)-DP(8 α ,9 α) (Figure). In relation to HC(8 β ,9 α), the DP(8 α ,9 α) conformation has the opposite sense of enone helicity, in accord with the change of signs of the $n \rightarrow \pi^*$ and long-wavelength $\pi \rightarrow \pi^*$ Cotton effects. The 11-oxo-derivative (4) retains all the chiroptical properties displayed by (3). The magnitudes of the $n \rightarrow \pi^*$ and long-wavelength $\pi \rightarrow \pi^*$ Cotton effects are higher in (4), but it is difficult to attribute this effect to any particular substituent in the 3 β -, 11-, or 14 α -position. It is of interest that 5-en-7-ones (1)-(4) with the 9 α ,10 β -configuration exhibit a strong negative short-wavelength $\pi \rightarrow \pi^*$ Cotton effect,¹⁶ irrespective of the presence of the 4,4-dimethyl systems, and in accord with the 'configurational rule' recently proposed for cyclohexanones.³

The reversal of configuration at C(9) and C(10) brings about, as expected, a change of overall geometry of the steroid skeleton. The torsion angle ϕ (6-5-10-9) takes a negative value and the skeleton in strain-free conformation contains ring *B* in HC(8 α ,9 β)-form. A ring *B* half-chair conformation has been assigned to Δ^5 -olefins with the 9 β ,10 α -configuration by ¹H n.m.r. studies,¹⁷ and a flattened half-chair conformation from an X-ray study of datiscoside (12).¹⁸ It should be noted that the ring *B* 9 β ,10 α configuration requires an 'inverted chair' conformation of ring *A* in order to release the strain. In such cases ¹H n.m.r. spectra prove the equatorial position of the 3 α -hydrogen atom. In the spectra of compounds (5)-(9) the signal of the 3 α -proton appears as a broadened singlet of half-width *ca.* 5 Hz,^{1,8} in contrast to broad multiplets observed for compounds having the 9 α ,10 β -configuration. The 'inverted chair' ring *A* conformation is demonstrated in yet another way in the diketone (10). Here, the β,γ -unsaturated 3-ketone displays a strong negative $n \rightarrow \pi^*$ Cotton effect

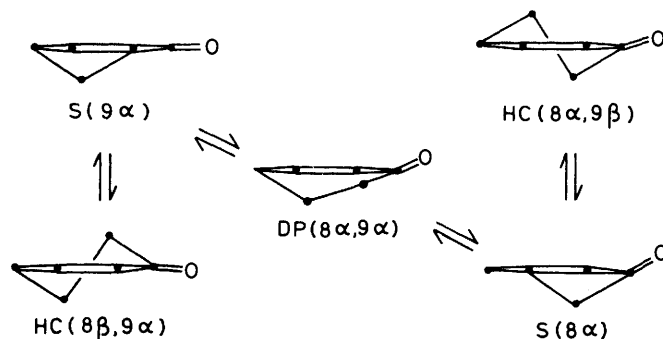


Figure. Ring *B* conformations in 5-en-7-ones: S = sofa, HC = half chair, DP = 1,3-diplanar

($\Delta\epsilon - 3.58$ at 293 nm), while 'normal chair' 4,4-dimethyl-5-en-3-ones are characterized by a positive $n \rightarrow \pi^*$ Cotton effect.¹⁹ Thus, the absolute conformation of the β,γ -unsaturated ketone chromophore is of enantiomeric type in both cases. Our c.d. data on 9 β ,10 α -5-en-7-ones (5)-(10) demonstrate a consistently negative $n \rightarrow \pi^*$ Cotton effect and a strong positive long-wavelength $\pi \rightarrow \pi^*$ Cotton effect, behaviour observed for 4-en-3-ones in HC(1 α ,2 β)-S(2 β) conformations.³ It thus follows that the ring *B* conformation in (5)-(10), if taken as HC(8 α ,9 β)-S(8 α), is indeed compatible with the c.d. data. Large long-wavelength $\pi \rightarrow \pi^*$ Cotton effects in (5)-(10) suggest considerable non-coplanarity of the enone chromophore, further supported by the weak (*i.e.* not observed as a separate peak) short-wavelength $\pi \rightarrow \pi^*$ Cotton effect. The apparent lack of the short-wavelength $\pi \rightarrow \pi^*$ Cotton effect has been noted in related 4-en-3-ones with large enone skew angles.³

The c.d. data for the 9 β ,10 β -5-en-7-one (11) do not differ considerably from those of (4)-(10), except for a slightly larger long-wavelength $\pi \rightarrow \pi^*$ Cotton effect in (11), suggesting the dominance of the highly skewed conformer S(8 α) in the equilibrium. It is appropriate to note here that (6) and (11) give different ¹H n.m.r. signal patterns for the 3 α -hydrogen atom and thus have different ring *A* conformations.⁸ In (11) flattening of ring *B* in the S(8 α) conformation around the ring *A/B* junction causes ring *A* to take up a distorted chair conformation with the 3 α -hydrogen atom close to the axial position. The upfield shift of the axial 3 α -proton signal in (11) (δ 4.60) as compared with (6) (δ 4.82) supports the assignment.

Experimental

C.d. spectra were recorded at room temperature with a Jobin-Yvon Dichrograph Mark III for solutions in acetonitrile at a concentration of *ca.* 1 mg in 10 ml and with a pathlength of 1 cm.

Acknowledgement

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